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13. SUPPLEMENTARY NOTES

14. ABSTRACT

The overall goal of this study is to use volumetric MRI to define the natural history of untreated plexiform neurofibromas in patients with NF1. Recruitment has been completed, including patients with head and neck or trunk and extremity plexiform neurofibromas, with serial MRI studies done over a three year period. Volumetric analysis is nearly completed, delayed by a two year hiatus in the study when the PI moved from Boston to Birmingham. In addition to completing the volumetric analysis, we plan to validate the volumetric data by complete review of all MRIs done on all patients, and use of two independent approaches to volumetric analysis. This will insure that data on tumor volumes is reliable, given that several years have elapsed between initial and final studies. It will also link the data in the present study to two ongoing initiatives: the NF Consortium, which is conducting clinical trials, and the Children's Tumor Foundation funded plexiform neurofibroma imaging repository.

15. SUBJECT TERMS
NF1, neurofibroma, plexiform, MRI, volumetric imaging

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Introduction

The overall aim of this study is to determine the rate of growth of untreated plexiform neurofibromas in patients with NF1 using volumetric MRI. The study underwent a hiatus from 2004-2006 due to the move of the PI from Children's Hospital/Brigham and Women's Hospital in Boston to University of Alabama at Birmingham. Recruitment had been closed prior to this time, but after the funding was transferred to UAB in 2006 it was necessary to re-establish all of the subcontracts with the multiple collaborating groups around the world. In addition, staff at WorldCare, the company responsible for the analysis of the MRI data, had changed and needed to be retrained to correctly interpret the MRIs of plexiform neurofibromas. Finally, each of the participating centers had to be contacted to update clinical and MRI data. These tasks occupied this entire year, with the result that almost all of the MRIs have been processed for volumetric analysis, but pending the completion of volumetric measurements, we have not performed the final statistical analysis. In addition, given the long gap in the study and the turnover of personnel in the MRI analysis unit, we feel it is necessary to reanalyze the volumetric data for scans obtained earlier in the study, in order to insure that consistent analysis has been obtained. Otherwise, there is a risk that different observers would have interpreted scans differently, leading to inconsistencies in the assessment of tumor volumes. As will be described below, we plan to reanalyze the data using three independent approaches, in order to insure that our assessment of the rate of tumor growth is valid. Because of the need to complete and validate the analysis, we have requested a no-cost extension for this year, during which we expect to complete all measurements and analysis and prepare for publication a final report of the study.

Body

Progress Report for Statement of Work by Task

Task 1. **Complete development of study infrastructure – Months 1-6**

a. **IRB approval at all clinical sites**

Table 1 lists the participating clinical centers, the principal investigator at each site, and the IRB approval status. University of Alabama at Birmingham, the current institution of the PI, was never a patient recruitment site, but does have an active IRB protocol in place to cover data analysis.

Table 1. Current status of IRB approval for project at participating centers.

Site ID	Site Name	PI	Status	IRB Information Updated
A-08394.a	Children's Hospital Boston	Mira Irons	Closed	Yes
A-08394.b	University of Utah	David Viskochil	Open	Yes
A-08394.c	New Children's Hospital Australia	Kathryn North	Open	No Continuing Review
A-08394.d	University of British Columbia	Jan Friedman	Closed	Yes
A-08394.e	Washington University Medical Center	David Gutmann	Open	Yes
A-08394.f	Massachusetts General Hospital	Scott Plotkin	Closed	No
A-08394.g	Mount Sinai Hospital	David Wolfe	Closed	Never enrolled patients
A-08394.h	Universitair Ziekwnhuis Gasthuisberd	Eric Legius	Closed	Never enrolled patients
A-08394.i	Cincinnati Children's Hospital Medical Center	Robert Hopkin	Open	Yes
A-08394.j	Children's Memorial Hospital	Joel Charrow	Closed	No
A-08394.k	Baylor College of Medicine	Sharon Plon	Open	Yes
A-08394.l	Guy's Hospital of London	Rosalie Ferner	Open	No Continuing Reviews
A-08394.m	University of Oklahoma Health Science Center	John Mulvihill	Open	Yes
A-08394.n	Children's National Medical Center	Roger Packer	Closed	Sent directly to Army
A-08394.o	Klinikum Nord Ochsenzoll	Victor-Felix Mautner	Closed	No
A-08394.p	Oxford University	Susan Huson	Closed	Never Enrolled Patients
A-08394.q	University of Sao Paulo	Fernando Kok	Closed	Never enrolled patients
A-08394-r	National Cancer Institute	Brigitte Widemann	Open	Yes
A-08394-s	Mayo Clinic	Dusica Babovic-Vuksanovic	Closed	Never enrolled patients

b. **Complete clinical data entry forms and test electronic transfer of clinical data**

Data entry forms were completed by the end of the first year, and have not changed.

c. **Organize package of materials for pathology review and tissue repository**

This task was completed by the end of the second year and has not changed.

d. **Set up listserv and website**

The study website is operational at www.nfstudies.org.

e. **Test MRI data transfer**

All testing and data transfer are completed.

f. **Purchase workstation and prepare data entry forms at WorldCare.**

The workstation was purchased in November of 1998.

g. **Prepare project monitoring flow sheet.**

All data have been entered into a new database customized for the project using StudyTrax software.

h. **Prepare recruitment letters for study subjects**

All recruitment is completed.

i. **Publicize study to NF community**

Publicity about the study has ceased since recruitment was halted. We plan an announcement of study outcomes after all data analysis is completed.

Task 2. ***Recruitment of Study Subjects*** **– Months 6-24**

a. **Centers contact prospective study subjects**
b. **Enrollment of study subjects**
c. **First MRI and clinical data received**

The status of recruitment is indicated in Table 2. As has been described in previous reports, recruitment was more problematic than expected, especially for adults. There are various reasons that participants did not complete the study; these included development of tumors requiring further treatment (surgery, radiation, chemotherapy) and participants who were lost to follow-up. Data analysis will be based on the set of patients who have completed the study.

Study Category	Number Recruited	Completed Study
Head & Neck < 18 Years old	65	**43**
Head & Neck > 18 Years old	27	**13**
Trunk & Extremity < 18 Years old	89	**57**
Trunk & Extremity > 18 Years old	81	**48**
Total	**262**	**161**

Table 2. Number of subjects recruited by study category.

d. **Review of clinical entry criteria**

This was completed in 2002 and is no longer relevant since the study is closed to recruitment.

e. **Test of inter-observer reproducibility of designation of tumor margins by MRI**

Results of this study were previously reported. A paper on this topic was published in the American Journal of Radiology. (*Interobserver Reproducibility of Volumetric MR Imaging Measurements of Plexiform Neurofibromas* Tina Young Poussaint, Diego Jaramillo, Yuchiao Chang, and Bruce Korf AJR 2003; 180: 419-423).

Task 3. ***Data Acquisition and analysis*** **– Months 13-42**

All of the MRI data has been received at WorldCare and WorldCare technologists have completed the volumetric measurements. All but 20 of these scans have been verified by the study radiologists. The 20 remaining to be analyzed are all trunk and extremity tumors. Analysis of these has been complicated by the fact that the study radiologist is no longer in Boston, and therefore must travel to Boston to review these scans. He has made two trips for this purpose during this past year, but was unable to complete the analysis of the last 20 scans during the final trip. It is expected that this will be completed by the end of the calendar year 2007. At that time, all of the volumetric analysis at WorldCare will have been completed and reviewed, at which time the data will be submitted to the study statistician for final analysis. We had performed an interim analysis in 2004 which was reported

in the progress report at that time. We did not feel it productive to do another interim analysis with the current data, since final analysis will be done after completion of the measurement of the last 20 scans.

Future Analysis

As noted in the introduction, the long hiatus in the project has not only delayed the final data analysis, but also complicated it by virtue of a long period of time having passed between analysis of the first MRI scans and final scans for each patient. Also, the technologists have changed during that time (although the radiologists who confirm the measurements have not). This raises an important question about data quality that will be critical to address. We have spent most of this past year re-establishing subcontracts and training technologists, and data analysis will be complete by the end of the calendar year. In order to insure that data quality is reliable, we plan three checks to insure that volumetric measurements have been done accurately:

1. Each study radiologist will perform a final review of all scans for each patient, insuring that tumor boundaries were identified in a consistent manner in all scans, in spite of different technologists having drawn the boundaries.
2. An independent radiologist, Dr. Gordon Harris of Massachusetts General Hospital, will reanalyze the data from all scans using a similar, but distinct, software system for volumetric analysis. Dr. Harris is funded by the Children's Tumor Foundation to provide routine volumetric analysis of plexiform neurofibromas and an imaging repository.
3. A third method, using a semi-automated system developed at the National Cancer Institute by Drs. Brigitte Widemann and Eva Dombi, will be used to verify all of the volumetric data. This analysis has the further advantage that it is the same as currently is being used in the NF Consortium clinical trials, which will make the volumetric analysis performed in the natural history study directly comparable with the methods now being used in the clinical trials consortium.

KEY RESEARCH ACCOMPLISHMENTS

- Publication of reproducibility study, demonstrating reliability of volumetric MRI approach. (*Interobserver Reproducibility of Volumetric MR Imaging Measurements of Plexiform Neurofibromas.* Tina Young Poussaint, Diego Jaramillo, Yuchiao Chang, and Bruce Korf AJR 2003; 180: 419-423)
- Publication of two papers on imaging characteristics of plexiform neurofibromas, and submission of a third manuscript
- Entry of all study data into a new database system (StudyTrax)
- Completion of all MRI initial measurements and radiologist confirmation of more than 90% of scans
- Arrangements made for verification of volumetric data by two independent approaches to insure data quality

REPORTABLE OUTCOMES

1. Manuscripts: see references.

2. Presentations: No recent presentations given that data analysis is incomplete.

3. Patents, licenses: none

4. Degrees obtained: not applicable

5. Tissue Repositories: A repository of blood and tumor tissue is now established at Washington University, St. Louis. This repository was initiated as part of this project, but is now being used by treatment protocols for pirfenidone and farnesyl transferase inhibitor, as well.

6. Informatics: The NF International Database has been modified to accommodate the specialized data collection required for use in this project. This database is open to investigators anywhere in the world (to input their own data, or query the database in a manner that preserves the confidentiality of patients. All study data has now been transferred to a new database using the StudyTrax system.

7. Employment/research opportunities: not applicable

CONCLUSION

The completion of this study has been significantly delayed due to the very long period of time required to transfer the study following the move of the PI from Boston to Birmingham. Much of the past year was spent in re-establishing the study subcontracts and retraining technologists to perform volumetric analysis. This process is complete, and final analysis of the data are nearly complete. As a result of the long hiatus, however, we believe it is necessary to verify the volumetric data to insure that consistent measurements were obtained by multiple observers over a long period of time. This will be critical if the study is to yield reliable natural history data. We have made the necessary arrangements and have sufficient funds in the contract to accomplish this. It is our plan to complete all of these steps in the upcoming year and then issue the final report and publish the outcomes of the study.

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